—Regular Articles—

A Method for Estimating Infection Route and Speed of Influenza

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(Received August 10, 2005; Accepted December 21, 2005; Published online December 22, 2005)

This paper puts forward a method for estimating the infection route and speed of influenza from the daily variations in the amount of influenza formulations supplied at distant city pharmacies. The cross-correlation function between the time variations at the pharmacies indicates as for the drug sales, how many days a pharmacy lags behind another pharmacy. The comparison of the time lags between the pharmacies can lead to the estimation of the infection route of influenza. Taking into account the distance between the locations of the pharmacies, we can calculate the infection speed of influenza. Three pharmacies located in Tokyo and its vicinity (Saitama and Kanagawa) are taken as an example. The thrust of this paper is to introduce the new strategy that can take full advantage of the information every pharmacy has in possession.

Key words——correlation; pharmacy; influenza; spectral analysis

INTRODUCTION

Spectral analysis is a methodology to study the stochastic properties of random processes or time series in a mathematical way.[1)] In medical sciences, there can be found many relevant publications in literature.[2—7)] For example, the power spectral densities of measles notifications were examined in several communities in Denmark, UK and USA.[7)] However, there have been published only a few related papers in pharmaceutical sciences.[8,9)]

The present paper applies a mathematical technique of spectral analysis (cross-correlation function) to the information inherent to pharmacies, *i.e.*, time variations in the amount of drug sale. A typical application of the technique to a meteorological problem concerns the relationship between the precipitation in a mountain area and the water level at the lower reaches of a stream.[1)] Their cross-correlation function has its maximum when the correlation is the strongest. Because of the definite causality between the precipitation and water level, the maximum implies the time delay between the two phenomena.

If a time delay is discovered in the cross-correlation function between the influenza prescriptions at distant pharmacies, we will be able to assess the route and speed of influenza infection in a district. This is because the cause of the delay can be the finite speed of infection from person to person in a society (assumption).

It is probable that the health conditions of people are reflected by the daily variations in the prescriptions at a pharmacy of the area where they live. This paper is an attempt to make the extensive vigilance of people's health on the basis of the information network among a large number of pharmacies. The idea of the nationwide surveillance is not new. For example, the information on influenza patients at hospitals in Japan is provided by Infectious Disease Surveillance Center and ML Influenza Ryukou Zensen Jouhou DB. To the authors' knowledge, however, the explicit utilization of the pharmaceutical information is first put forward by this paper.

METHODS

The information about the prescriptions of drugs was collected from the pharmacies at and around Tokyo: Homecare Pharmacy Hanno, 21–5 Shinmachi, Hanno, Saitama; Tanashi Honcho Pharmacy, 4–25–5 Tanashi, Nishi-Tokyo, Tokyo; Tanashi Kodomo Pharmacy, 4–24–18 Tanashi, Nishi-Tokyo, Tokyo; Homecare Pharmacy Yokohama, 1268–103 Shinohara, Kouhoku-ku, Yokohama, Kanagawa. The pharmacies were open throughout the year and the data of weekends were also available. The two pharmacies in Nishi-Tokyo are located near emergency hospitals, and the other pharmacies are near clinics (but not emergency ones).

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CALCULATION

In general, the cross-correlation function between time series, $A(t)$ and $B(t)$, is defined as:[1)]

$$R(\tau)=\frac{E[A(t)B(t+\tau)]}{\sqrt{E[A(t)^2]E[B(t)^2]}} \qquad (1)$$

where $E[.]$ denotes the mean over time t of the random variables inside the square brackets and τ is the lag. Equation 1 has the maximum when the correlation between $A(t)$ and $B(t+\tau)$ is the maximum among all the possible τ. Therefore, Eq. (1) is a function of τ. The cross-correlation function is not necessarily symmetrical with respect to the lag, τ, but asymptotically approaches to zero, when τ is infinite.[1)] In Figs. 2, 4 and 6, the cross-correlation functions are calculated from the data of 365-τ days.

RESULTS AND DISCUSSION

Figure 1 shows the time series of the prescriptions of an influenza anti-viral agent (Tamiflu Dry Syrup 3 %, Chugai Pharmaceutical Co., Ltd.) from November 1st in 2003 to October 31st in 2004 (366 days; intercalary year) at the pharmacies located at (A) Hanno, (B) Nishi-Tokyo and (C) Yokohama. As is well-known, the influenza is prevalent from December to March and in turn the drug is supplied over the period. The trends of the time series look similar in Figs. 1(A)–1(C), although the absolute values of the prescribed amounts are much different due to the populations of the cities and scales of the pharmacies. The signals which look like spike noises are the hebdomadal frequency of the prescriptions.

From Fig. 1, we can easily guess that the time series of the prescriptions are more or less synchronized between the different sites. This paper uses the cross-correlation function for quantitative consideration.

Figure 2(A) shows the cross-correlation function between the time series at Hanno and Yokohama. The maximum of the correlation function is located at −7 days (=τ). This result indicates that the time series of Tamiflu prescriptions of the pharmacy at Hanno lags seven days behind that at Yokohama.

Geographically, Nishi-Tokyo is located between Hanno and Yokohama. Figure 2(B) shows the cross-correlation function between the time series at Hanno and Nishi-Tokyo. The maximum correlation occurs at the time lag of −3 days. Similarly, the cross-correlation function between Nishi-Tokyo and Yokohama has the maximum at $\tau=-4$ days (*see* Fig. 2(C)).

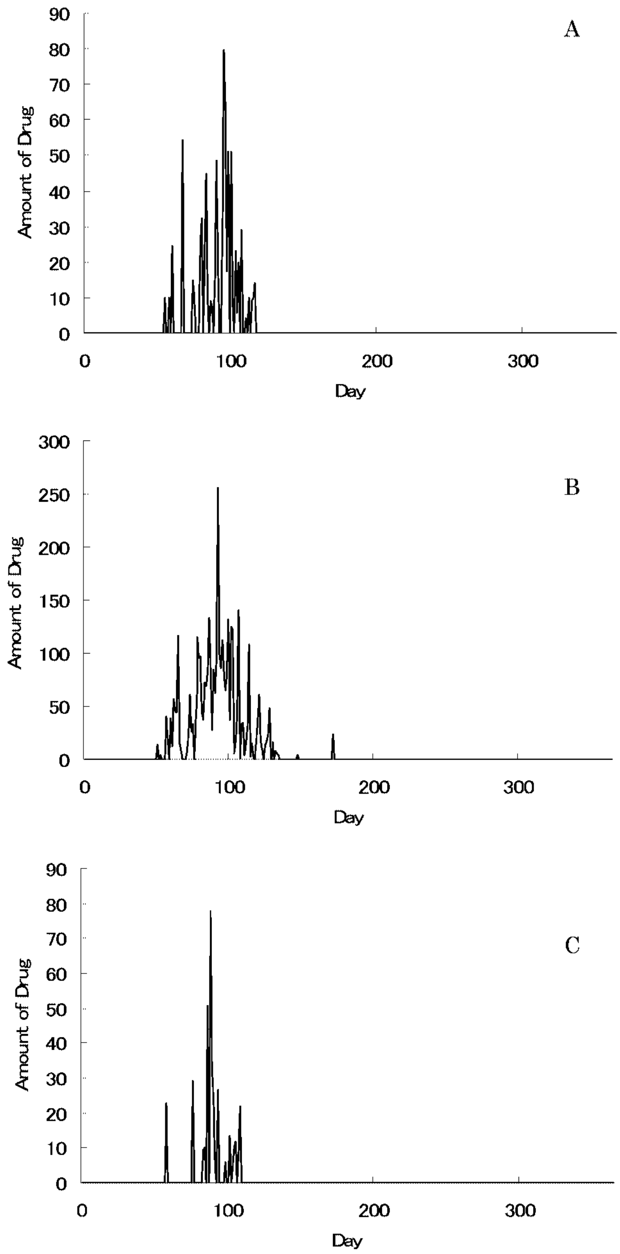

Fig. 1. Time Series of Influenza Prescriptions for Children (Tamiflu Dry Syrup 3%) from November 1st in 2003 to October 31st in 2004 (366 days)

Y axis: gram. Pharmacies: (A) Homecare Pharmacy Hanno at Hanno, (B) Tanashi Honcho Pharmacy at Nishi-Tokyo, (C) Homecare Pharmacy Shin-Yokohama at Yokohama.

The straightforward interpretation of the results of Fig. 2 leads to the infection route and speed of influenza. In the present paper, however, the resulting route and speed are not accurate estimates (*see* below) and the following logic is presented for the sake of explanation. The results of Fig. 2 can be illustrated as:

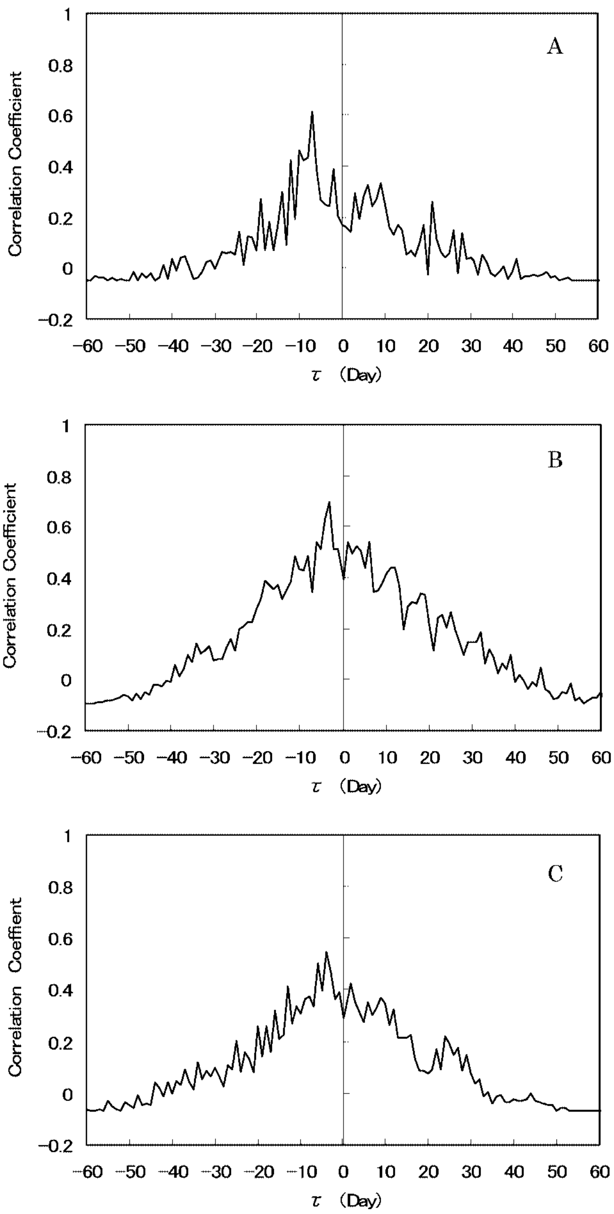

Fig. 2. Cross-correlation Functions between Influenza Prescriptions (Tamiflu Dry Syrup 3%) at Distant Sites

A: cross-correlation function between Hanno and Yokohama (A and C of Fig. 1), B: Hanno and Nishi-Tokyo (A and B of Fig. 1), C: Nishi-Tokyo and Yokohama (B and C of Fig. 1).

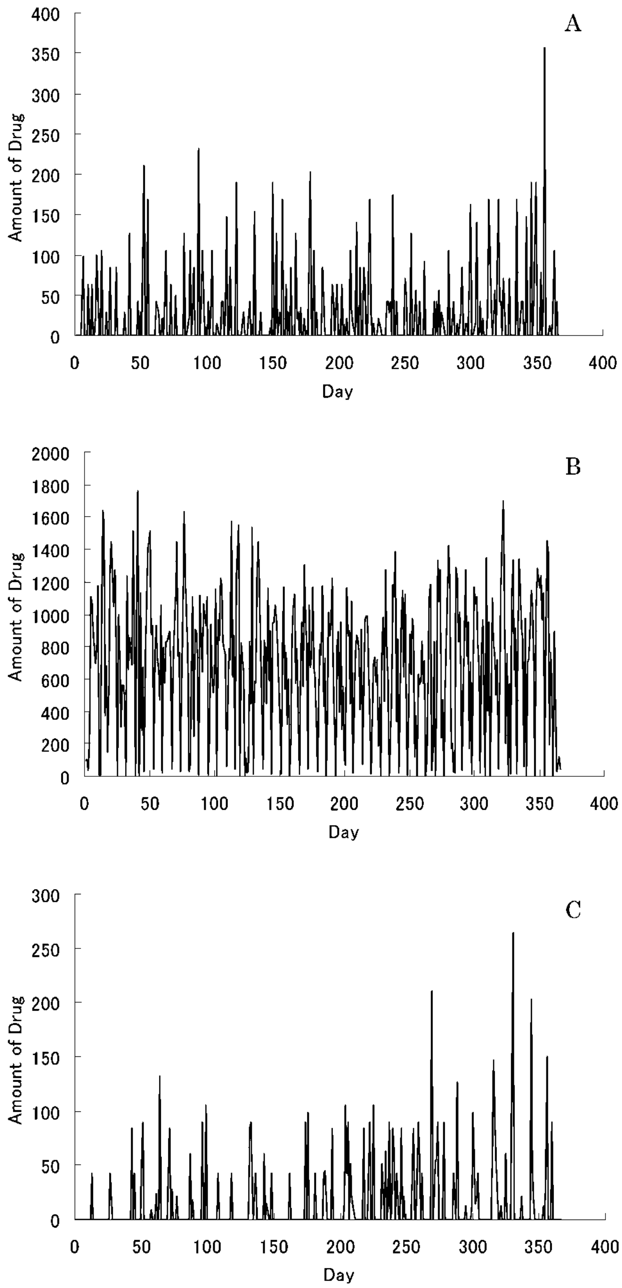

Fig. 3. Time Series of Gastritis and Gastric Ulcer Treatment (Selbex) from January 1st to December 31st in 2004 (366 days)

Y axis: capsules. Pharmacies: (A) Homecare Pharmacy Hanno at Hanno, (B) Tanashi Honcho Pharmacy at Nishi-Tokyo, (C) Homecare Pharmacy Shin-Yokohama at Yokohama.

Yokohama —(4 days)→ Nishi-Tokyo —(3 days)→ Hanno

Yokohama —(7 days)→ Hanno

Noticing that influenza is an infectious disease, we can expect that the time lag of the cross-correlation function of the prescriptions at the distant pharmacies leads to the apparent infection route, Yokohama →Nishi-Tokyo→Hanno. Since the distance between Hanno and Yokohama is about 48 km, the infection speed can be calculated to be about 7 km/day. The time lags between the monitoring sites cannot be calculated directly from the time series of Fig. 1, and the cross-correlation function is a powerful tool for this purpose.

The above results of the time lags (Fig. 2) are not accidental. Figure 3 shows the time variation in the daily prescriptions of a gastritis and gastric ulcer treatment (Selbex Capsules 50 mg, Eisai Co., Ltd.) at the pharmacies located at (A) Hanno, (B) Nishi-Tokyo and (C) Yokohama. Unlike the influenza antiviral agent (*see* Fig. 1), the prescriptions are made up almost constantly throughout the year and are not restricted within a period of year.

Figure 4 shows the cross-correlation functions between the distant sites: (A) Hanno and Yokohama; (B) Hanno and Nishi-Tokyo; (C) Nishi-Tokyo and Yokohama. No conspicuous cross-correlations are found in Fig. 4 for the non-infectious disease. The infection of a disease is essential for the strong correlation between the distant sites as shown in Fig. 2.

Figure 5 shows the time series of the influenza antiviral agent (Tamiflu) at a pharmacy (Tanashi Kodomo Pharmacy) which is located near the pharmacy mentioned above (Tanashi Honcho Pharmacy). They are about 100-meter away. The time series of the daily prescriptions resemble each other (compare Figs. 5 and 1 (A)). Figure 6 shows the strong correlation between the time series at the nearby pharmacies. However, no clear time lag can be spotted in the cross-correlation function. The distance of the observation sites is an indispensable factor for the time lag

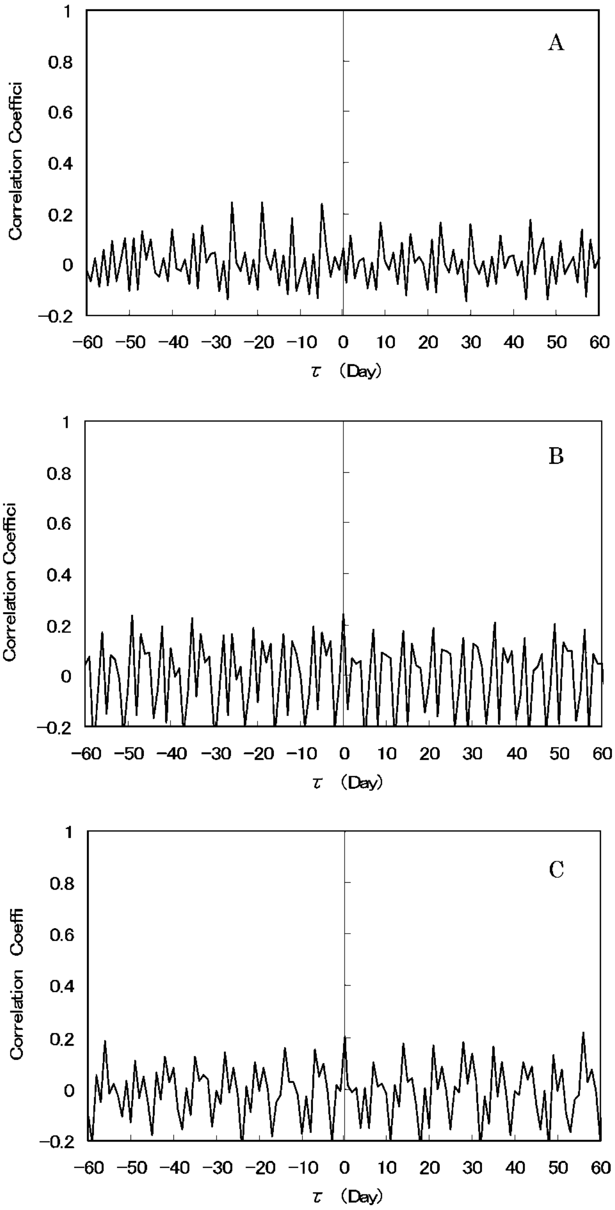

Fig. 4. Cross-correlation Functions between the Prescriptions of Gastritis and Gastric Ulcer Treatment (Selbex) at Distant Sites

A: cross-correlation function between Hanno and Yokohama (A and C of Fig. 3), B: Hanno and Nishi-Tokyo (A and B of Fig. 3), C: Nishi-Tokyo and Yokohama (B and C of Fig. 3).

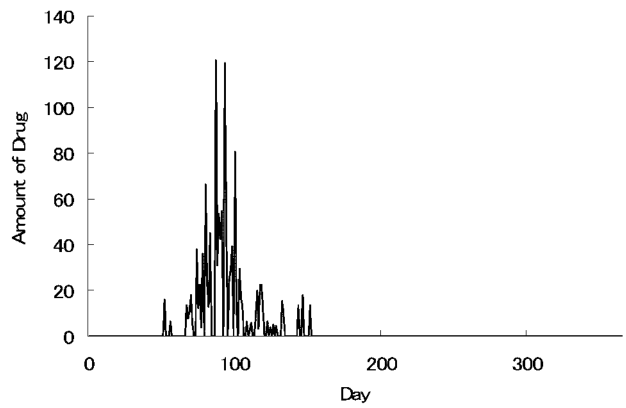

Fig. 5. Time Series of Influenza Prescriptions for Children (Tamiflu Dry Syrup 3%) from November 1st in 2003 to October 31st in 2004 (366 days)

Y axis: gram. Pharmacy: Tanashi Kodomo Pharmacy at Nishi-Tokyo.

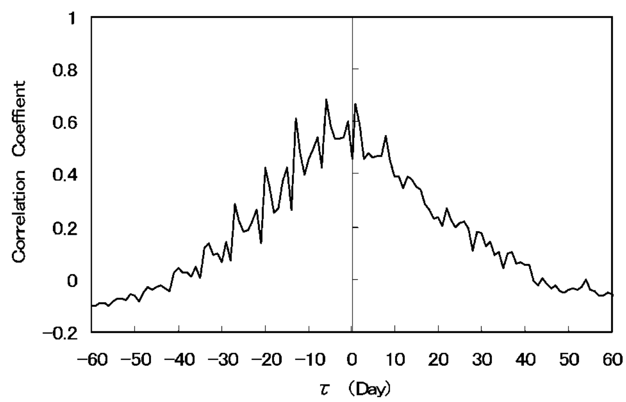

Fig. 6. Cross-correlation Function between Influenza Prescriptions (Tamiflu Dry Syrup 3%) at nearby Pharmacies

Cross-correlation function between the time series of Fig. 1 (B) and Fig. 5. Pharmacies: $A(t)$ = Tanashi Honcho Pharmacy and $B(t)$ = Tanashi Kodomo Pharmacy at Nishi-Tokyo.

of the maximum correlation.

The hebdomadal cycles occurring in the time series of Fig. 1 could disturb the correct determination of the time lags in Fig. 2. A smoothing method (moving average method with 7 days intervals) was applied to the cross-correlation functions to remove the cycles. The functions were smoothed accordingly (not shown), and the results were the same as those of Fig. 2.

Another influenza anti-viral agent (Tamiflu Capsule, Chugai Pharmaceutical Co., Ltd.) had the time lags which are similar to those of Fig. 2 (not shown). The capsules are usually administered to adults and the dry syrup to children. This subject will be taken in the next paper.

CONCLUSION

This paper has presented an approach to take full advantage of the information every pharmacy holds in possession. The infection route and speed of influenza have been estimated by the cross-correlation functions between the time series of the prescriptions at pharmacies in Saitama, Tokyo and Kanagawa. However, this estimation is too rough to describe the real infection pattern, since the number of observation sites is minimum (=3) and the information sources are limited to city pharmacies alone. In-depth consideration of infection pattern will not be possible, until the information network among a large number of pharmacies, drugstores, hospitals, clinics, etc. over a wide area will be constructed. The purpose of this paper is to propose the new method.

One of the advantages of the present method is that no personal information such as ages and occupations is necessary for the analysis and the method does not violate Act on the Protection of Personal Information.

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